CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPI
International B

WO 9601625A1

INTERNATIONAL APPLICATION PUBLISHED UNDER

(51) International Patent Classification 6 :		(11) International Publication Number:
A61K 9/26, 9/20, 31/44	A1	WO 96/01625
		(43) International Publication Date: 25 January 1996 (25.01.96)

(21) International Application Number: PCT/SE95/00680

(22) International Filing Date: 7 June 1995 (07.06.95)

(30) Priority Data:
9402431-2 8 July 1994 (08.07.94) SE

(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BERGSTRAND, Pontus, John, Arvid [SE/SE]; Walleriusgatan 4, S-412 58 Göteborg (SE). LÖVGREN, Kurt, Ingmar [SE/SE]; Violinvägen 2D, S-435 44 Mölnlycke (SE).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: MULTIPLE UNIT TABLETED DOSAGE FORM CONTAINING PROTON PUMP INHIBITOR

(57) Abstract

A new pharmaceutical multiple unit tableted dosage form containing an acid labile, pharmaceutically active substance with gastric inhibitory effect, or one of its single enantiomers or an alkaline salt thereof, a method for the manufacture of such a formulation, and the use of such a formulation in medicine.

* (Referred to in PCT Gazette No. 13/1996, Section II)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/26, 9/20, 31/44

A1

(11) International Publication Number: **WO 96/01625**

(43) International Publication Date: 25 January 1996 (25.01.96)

(21) International Application Number: PCT/SE95/00680

(22) International Filing Date: 7 July 1995 (07.07.95)

(30) Priority Data:
9402431-2 8 July 1994 (08.07.94) SE

(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BERGSTRAND, Pontus, John, Arvid [SE/SE]; Walleriusgatan 4, S-412 58 Göteborg (SE). LÖVGREN, Kurt, Ingmar [SE/SE]; Violinvägen 2D, S-435 44 Mölnlycke (SE).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: MULTIPLE UNIT TABLETED DOSAGE FORM CONTAINING PROTON PUMP INHIBITOR

(57) Abstract

A new pharmaceutical multiple unit tableted dosage form containing an acid labile, pharmaceutically active substance with gastric inhibitory effect, or one of its single enantiomers or an alkaline salt thereof, a method for the manufacture of such a formulation, and the use of such a formulation in medicine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

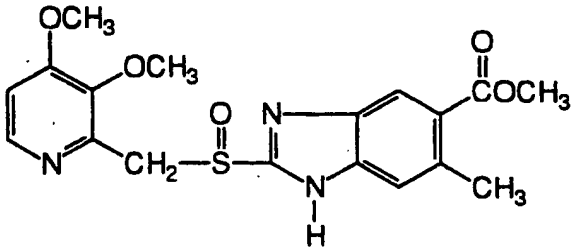
Multiple unit tabletted dosage form containing proton pump inhibitor.

Field of the invention

The present invention is related to new pharmaceutical preparations in the form of a multiple unit tableted dosage form comprising acid labile heterocyclic compounds or one of its single enantiomers or alkaline salts thereof with gastric acid inhibitory effect. The novel tableted dosage form is intended for oral use. Furthermore, the present invention refers to a method for the manufacture of such preparations and, to the use of such preparations in medicine.

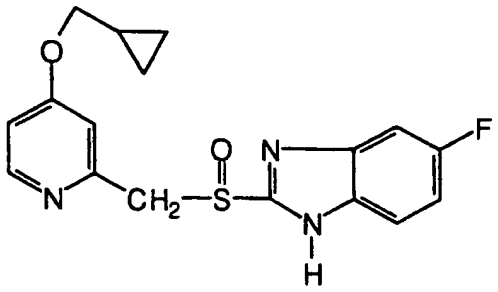
Background of the invention

Acid labile heterocyclic compounds with gastric inhibitory effect are for instance compounds described in EP-A1-0005129, WO 90/06925 and WO 91/19712. The following compounds I and II are of specific interest for the novel tableted dosage form according to the present invention



I

5-Carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl-1H-benzimidazole and



II

5-Fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

Compounds I and II used in the compositions of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+}, Ca^{2+}, Na^{2+} or K^{+} salts, preferably Mg^{2+} salts. These compounds may be used in racemic form or in the form of one of its single enantiomers. The latter are described in PCT/SE 94/00510 and PCT/SE 94/00511 both filed on May 27, 1994.

These active substances are, as already mentioned, useful for inhibiting gastric acid secretion in mammals and man. In a more general sense, they may be used for prevention and treatment of gastric acid related diseases in mammals and man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, they may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. They may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent acid aspiration of gastric acid and to prevent and treat stress ulceration. Further, they may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these.

These compounds with gastric inhibitory effect are, however, susceptible to degradation/transformation in acidic and neutral media. The degradation is catalyzed by acidic compounds and they are usually stabilized in mixtures with alkaline compounds. The stability of the compounds is also affected by moisture, heat, organic solvents and to some degree by light.

In respect to the stability properties of these acidic susceptible compounds, it is obvious that the active compound in an oral solid dosage form must be protected from contact with the acidic gastric juice and must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption of the pharmaceutically active substance can occur.

A pharmaceutical oral dosage form of the specific active compound is best protected from contact with acidic gastric juice by an enteric coating layer. In US-A 4,853,230 enteric coated preparations of acid labile substances are described. Said preparations contain an alkaline core comprising the active substance, a separating layer and an enteric coating layer. In order to further enhance the stability during storage the prepared formulation may optionally be packed with a desiccant.

There has been a demand for development of new enteric coating layered multiple unit preparations with good chemical and mechanical stability making it possible to produce well functioning and patient-friendly packages, such as for instance blister package. Furthermore, there is a demand for formulations having an improved patient acceptance, such as divisible and/or dispersible tablets.

A good mechanical stability can be obtained with an enteric coating layered tablet (WO 95/01783 describes such a tablet comprising the acid labile compound, omeprazole). However, only an enteric coating layered multiple unit tablet can be made divisible and dispersible. A further advantage of a multiple unit dosage

form is that it disperses into a multitude of small units in the stomach upon administration.

Prior art discloses many different types of multiple unit dosage forms. Usually this type of formulation is requested for controlled release formulations, such as sustained release formulations. Typically, the multiple unit formulation may be a tablet which disintegrates in the stomach to make available a multitude of coated units, or pellets filled in a capsule. (See for example EP 0 080 341 and US-A 4,853,230).

An example to obtain a controlled release dosage form releasing the active substance by diffusion through a membrane is described in US-A 4,927,640, i.e. a multiple-unit system containing small inert cores coated with active substance and a release controlling polymeric membrane. The mechanical properties of such multiple units formulated into tablets are reported in Pharmaceutical Research, 10 (1993), p. S-274. Other examples of controlled release dosage forms are for example described in Aulton M.E. (Churchill Livingstone), Pharmaceutics: The science of dosage form design (1988), p. 316-321.

Even if there are examples in the prior art mentioning that pellets may be formulated into tablets, there are no examples describing any compositions of such a tablet formulation or a technique to manufacture such a formulation comprising an acid labile substance. In practice, problems arise when enteric coating layered pellets, especially containing acidic susceptible substances are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be destroyed by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression. The above described problems are well illustrated in Reference Examples below.

Further, controlled release tablets from enteric coated particles are described in Drugs Made In Germany, 37 No. 2 (1994), p. 53. The teaching in this reference is that a combination of a methacrylic acid copolymer (L30D-55) and a copolymer of ethyl acrylate and methyl methacrylate (NE30D) is suitable as coating polymers for enteric coated particles compressed into tablets. Reference Example III shows that this recommendation is not applicable when formulating multiple unit tableted dosage forms of acidic susceptible substances. The acid resistance of the pellets compressed into a tablet is too low. The cited reference Drugs Made In Germany also states that the use of the copolymer L30D-55 without the addition of the copolymer NE30D as material for enteric coating layers will result in coated pellets which cannot withstand compression forces used during the tableting process. With reference to this statement it is surprisingly found that pellets covered with L30D-55 according to this invention, see Examples below, are possible to compress into tablets with fulfilled requirements including acceptable acid resistance of the tablet.

The Applicant is not aware of any working example in the prior art of a multiple unit tableted dosage form comprising an acid labile heterocyclic compound.

Description of the invention

The Applicant has now surprisingly found that tablets according to the present invention comprising enteric coating layered units containing an acid labile heterocyclic compound in the form of compound I or II, or one of its single enantiomers or an alkaline salt thereof can be manufactured by compressing said units into tablets without significantly affecting the properties of the enteric coating layer. As explained above, if the enteric coating layer is damaged during compression of the enteric coating layered units the acid resistance of said enteric coating layer in the manufactured tablet will not be sufficient and the manufactured tablets will not fulfill standard requirements on enteric coated

articles, such as e.g. those defined in the United States Pharmacopeia, hereby incorporated in a whole by reference. In the following the expression "compounds I and II, respectively" is including the single enantiomers of said compounds as well as an alkaline salt of said compound or of one of its single enantiomers.

One object of the present invention is to provide a pharmaceutical multiple unit tableted dosage form comprising compound I or II or one of its single enantiomers or an alkaline salt thereof, in which the active substance is in the form of individually enteric coating layered units compressed into a tablet. The enteric coating layer(s) covering the individual units of active substance has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating layered units. The active substance is prevented from degradation and dissolution in acidic media and has a good stability during long-term storage. The enteric coating layer covering the individual units disintegrates/dissolves rapidly in near neutral or alkaline media.

Another object of the present invention is to provide a pharmaceutical multiple unit tableted dosage form comprising compound I or II or one of its single enantiomers or an alkaline salt thereof which is suitable for press-through blister packages and which also has improved patient acceptance.

A further object of the present invention is to provide a multiple unit tableted dosage form comprising compound I or II or one of its single enantiomers or an alkaline salt thereof which is divisible and easy to handle. The multiple unit tableted dosage form may be dispersed in an aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed enteric coating layered units of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

Detailed description of the invention.

The novel multiple unit tableted dosage form comprising compound I or II or one of its single enantiomers or an alkaline salt thereof is characterized in the following way. Individually enteric coating layered units containing the active substance, and optionally alkaline substances, are mixed with tablet excipients and compressed into multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, particles, granules or pellets, in the following referred to as pellets.

The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness, of the enteric coating layer(s) must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished and that the acid resistance does not decrease more than 10 % during the compression of pellets into tablets.

The flexibility/hardness of enteric coating layers can be characterized for instance as Vickers hardness measured with a Shimadzu micro hardness indentation tester type HMV 2 000.

The acid resistance is defined as the amount of active substance in tablets or pellets after being exposed to simulated gastric fluid, USP, or to 0.1 M HCl(aq) relative to that of unexposed tablets or pellets, respectively. The test is accomplished in the following way. Tablets or pellets are exposed to simulated gastric fluid at a temperature of 37°C. The tablets disintegrate and release the enteric coating layered pellets to the medium. After two hours the pellets are removed and analyzed for content of active substance using High Performance Liquid Chromatography (HPLC). Presented values of acid resistance are averages of at least three individual determinations.

Core material

The core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with active substance in the form of compounds I and II, respectively, or one of its single enantiomers or an alkaline salt thereof, optionally mixed with alkaline compounds, can be used as the core material for the further processing.

The seeds, which are to be layered with the active substance, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise active substance in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention and may vary between approximately 0.1 and 2 mm. The seeds layered with active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.

Before the seeds are layered, the active substance may be mixed with further components. Such components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures. The binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and carboxymethylcellulose sodium, polyvinyl pyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the compounds I and II, respectively, optionally mixed with alkaline compounds and further mixed with suitable constituents can be

formulated into core material. Said core materials may be produced by extrusion/spheronization, balling or compression utilizing different process equipments. The size of the formulated core materials is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core materials can further be layered with additional ingredients comprising active substance and/or be used for further processing.

The active substance is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used.

The active substance may also be mixed with an alkaline pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

The active substance is in the form of 5-fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole, 5-carbomethoxy-6-methyl-2-[[(3,4-

dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole, respectively, or one of its single enantiomers or an alkaline salt thereof. These compounds have an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50 % of each enantiomer) and unequal mixtures of the two enantiomers are suitable for the pharmaceutical formulation according to the present invention.

Enteric coating layer(s)

Before applying enteric coating layer(s) onto the core material in the form of individual pellets, said pellets may optionally be covered with one or more separating layers comprising pharmaceutical excipients optionally including alkaline compounds such as for instance pH-buffering compounds. This/these separating layer(s) separate(s) the core material from the outer layer(s) being enteric coating layer(s).

The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for separating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the separating layer(s).

When the optional separating layer(s) is applied to the core material it may constitute a variable thickness. The maximum thickness of the optional separating layer(s) is normally only limited by processing conditions. The separating layer(s) may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other compounds may be added to increase the thickness of the layer(s) and thereby strenghten the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more separately or in combination of the following can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s).

The enteric coating layers contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s) for instance exemplified as Vickers hardness, are adjusted so that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during the compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments, polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acidic susceptible material.

To protect an acidic susceptible substance and to obtain an acceptable acid resistance of the multiple unit tableted dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 µm, preferably more than 20 µm. The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

Over-coating layer

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinyl-pyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethyl-cellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of coated pellets, further protect the enteric coating towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally only limited by processing conditions.

Tablets

The enteric coating layered pellets are mixed with tablet excipients and compressed into a multiple unit tableted dosage form according to the present invention. The enteric coating layered pellets with or without an over-coating layer are mixed with tablet excipients such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives and compressed into tablets. The compressed tablet is optionally coated with filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability

of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

The amount of enteric coating layered pellets constitutes less than 75% by weight of the total tablet weight and preferably less than 60 %. By choosing small enteric coating layered pellets in the formulation according to the present invention, the number of pellets in each tablet can be held high which in turn makes the tablet divisible with retained dosing accuracy.

The mechanical properties, i.e. the flexibility and hardness of the enteric coating layer are essential for the acid resistance of the multiple unit tableted dosage form. The flexibility/hardness of the enteric coating layer surface may be characterized as a preliminary process parameter in the form of Vickers hardness, measured on enteric coating layered pellet(s) before compression of said pellets into tablets. The Vickers hardness may be measured with a Shimadzu micro hardness indentation tester type HMV 2000 (Micro Hardness Testing Machines for Vickers and Knoop Hardness JIS B 7734-1984 and JIS Z 2251-1980). The ability of the enteric coating layer(s) to withstand compression into tablets is, of course, a function of both the amount of applied coating layer and the mechanical properties of said coating layer material. To obtain well functioning enteric coating layered pellets with a reasonable amount of enteric coating layer material and which pellets can be compressed into tablets without significantly affecting the acid resistance, an enteric coating layer surface with a Vickers hardness of less than 8 is preferred. In case the pellets are covered with an over-coating layer the Vickers hardness of the enteric coating layer must be characterized before the over-coating layer is applied. A harder over-coating layer (Vickers hardness higher than 8) can be applied on top of a flexible and softer (Vickers hardness less than 8) enteric coating layer with retained acid resistance during compaction.

Thus, the formulation according to the invention consists of core material containing active substance in the form of compounds I and II, respectively mixed with alkaline compound(s), and excipients. The addition of an alkaline material may not be necessary, but such a substance may further enhance the stability of the active substance. The core material is optionally covered with one or more separating layer(s) optionally containing alkaline substance(s). The pellets, optionally covered with a separating layer(s), are then covered with one or more enteric coating layer(s) making the pellets insoluble in acidic media, but disintegrating/dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted. The enteric coating layered pellets may further be covered with an over-coating layer before being formulated into the multiple unit tableted dosage form.

Process

The process for the manufacture of the dosage form represents a further aspect of the invention. The pharmaceutical processes can preferably be completely water-based and there are different descriptions given in the accompanying examples below.

Use of preparation

The preparation according to the invention is also especially advantageous in reducing gastric acid secretion. Such a multiple unit tableted dosage form is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the daily dose will be in the range of 1-1000 mg of active substance.

The preparation according to the present invention is also suitable for dispersion in an aqueous liquid with neutral or slightly acidic pH-value before being orally administered or fed through a naso-gastric tube.

The invention is illustrated more in detail by the following examples.

EXAMPLES

Example 1

Core material

5-Fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium	312 g
Sugar sphere seeds	300 g
Hydroxypropyl methylcellulose	80 g
Purified water	1 520 g

Separating layer

Core material	300 g
Hydroxypropyl cellulose	21 g
Talc	37 g
Magnesium stearate	2 g
Purified water	400 g

Enteric coating layer

Pellets covered with separating layer	300 g
Methacrylic acid copolymer	285 g
Triethyl citrate	85.5 g
Mono- and diglycerides	14 g
Polysorbate 80	1 g
Purified water	557 g

Tablets

Enteric coating layered pellets	150 g
Microcrystalline cellulose	349 g

Sodium stearyl fumarate	1 g

Solution layering is performed in a fluid bed apparatus using bottom spray technique. 5-Fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium is sprayed onto sugar sphere seeds from a water solution containing the dissolved binder. The size of sugar sphere seeds are in the range of 0.25 to 0.35 mm.

The prepared core material is covered with separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer is sprayed as a water dispersion onto the pellets covered with separating layer in a fluid bed apparatus. The Vickers hardness on enteric coating layered pellets is measured to a value of 2.

Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets using a single punch tableting machine using 12 mm round punches. Hardness of tablet measured on a Schleuniger hardness tester is determined to 95 - 116 N.

Example 2

Core material	
5-Carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole magnesium	600 g
Mannitol	1000 g
Microcrystalline cellulose	300 g
Hydroxypropyl cellulose	100 g
Sodium lauryl sulfate	6 g
Purified water	802 g
Separating layer	
Core material	400 g
Hydroxypropyl methylcellulose	48 g
Purified water	960 g

Enteric coating layer	
Pellets covered with separating layer	200 g
Methacrylic acid copolymer	100 g
Triethyl citrate	30 g
Mono- and diglycerides	5 g
Polysorbate 80	0.5 g
Purified water	309 g

Tablets	
Enteric coating layered pellets	200 g
Microcrystalline cellulose	299 g
Sodium stearyl fumarate	1.2 g

Sodium lauryl sulfate is dissolved in purified water to form the granulation liquid. 5-Carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole magnesium, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.

The wet mass is forced through an extruder equipped with screens, aperture size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered with separating layer in a fluid bed apparatus with a hydroxypropyl methyl-cellulose/water solution.

The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

Enteric coating layered pellets, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets with a tablet weight corresponding to 20 mg active substance, using a single punch tableting machine equipped with 10 mm round punches.

Example 3

Core material	
(-)-5-Carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole magnesium	600 g
Sugar sphere seeds	600 g
Hydroxypropyl methylcellulose	150 g
Colloidal silicon dioxide	4 g
Purified water	1 800 g
Separating layer	
Core material	500 g
Hydroxypropyl cellulose	40 g
Talc	67 g
Magnesium stearate	6 g
Purified water	800 g
Enteric coating layer	
Pellets covered with separating layer	500 g
Methacrylic acid copolymer	200 g
Triethyl citrate	60 g
Purified water	392 g
Tablets	
Enteric coating layered pellets	430 g
Microcrystalline cellulose	871 g
Sodium stearyl fumarate	3 g

(-)-5-Carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole magnesium, part of the hydroxypropyl methylcellulose and colloidal silicon dioxide are dry-mixed forming a powder mixture. Sugar sphere seeds (0.25-0.35 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).

The prepared core material is dried and covered with separating layer in a centrifugal fluidized coating granulator. A fluid bed apparatus is used for enteric coating layering.

Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets using a rotary tableting machine equipped with 6 pairs of 10 mm round punches. The amount of active substance in the tablet is approx. 20 mg.

Example 4

Core material	
(-)-5-Carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole	400 g
Silicon dioxide seeds	400 g
Hydroxypropyl methylcellulose	100 g
Sodium lauryl sulfate	2 g
Purified water	2 000 g
Separating layer	
Core material	800 g
Hydroxypropyl methylcellulose	65 g
Purified water	1 300 g
Enteric coating layer	
Pellets covered with separating layer	500 g
Methacrylic acid copolymer	300 g
Polyethylene glycol 400	60 g
Mono- and diglycerides	9 g
Polysorbate 80	1 g
Purified water	800 g
Tablets	
Enteric coating layered pellets	200 g
Microcrystalline cellulose	598 g
Sodium stearyl fumarate	2 g

Suspension layering is performed in a fluid bed apparatus. (-)-5-Carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole is sprayed onto the

seeds of silicon dioxide (size range 0.15 - 0.3 mm) from a water suspension containing the dissolved binder and a surface active ingredient.

The prepared core material is covered with separating layer in a fluid bed apparatus using a hydroxypropyl methylcellulose solution. The enteric coating layer material is sprayed as a water dispersion onto pellets in a fluid bed apparatus. Enteric coating layered pellets and the tableting excipients are mixed and compressed into tablets as described in Example 1.

Example 5

Enteric coating layer

Pellets covered with separating layer (manufacturing and composition as in Example 1)	500 g
Methacrylic acid copolymer	250 g
Polyethylene glycol 6000	75 g
Mono- and diglycerides	12.5 g
Polysorbate 80	1.2 g
Purified water	490 g

Tablets

Enteric coating layered pellets	600 g
Microcrystalline cellulose	1 395 g
Sodium stearyl fumarate	5 g

Enteric coated pellets, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets as described in Example 3.

Example 6

Enteric coating layer

Pellets covered with separating layer (manufacturing and composition as in Example 1)	400 g
Hydroxypropyl methylcellulose phthalate	400 g
Diethyl phthalate	80 g
Ethanol	1 600 g
Acetone	4 000 g

Tablets	
Enteric coating layered pellets	500 g
Microcrystalline cellulose	1 500 g
Magnesium stearate	5 g

Enteric coating layering is performed by spaying a solution in a fluid bed. Enteric coating layered pellets, microcrystalline cellulose and magnesium stearate are mixed and compressed into tablets as described in Example 3.

Example 7

Core material	
(+)-5-Fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole	400 g
Sugar sphere seeds (non-pareils)	400 g
Hydroxypropyl methylcellulose	80 g
Purified water	1 600 g

Separating layer	
Core material	800 g
Hydroxypropyl cellulose	40 g
Talc	40 g
Magnesium stearate	8 g
Purified water	800 g

Enteric coating layer	
Pellets covered with separating layer	800 g
Methacrylic acid copolymer	400 g
Triethyl citrate	120 g
Mono- and diglycerides	8 g
Polysorbate 80	1 g
Purified water	800 g

Tablets	
Enteric coating layered pellets	1 000 g
Dibasic calcium phosphate anhydrous	1 760 g

Microcrystalline cellulose	440 g
Magnesium stearate	16 g

Suspension layering is performed in a fluid bed apparatus. (+)-5-Fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.
The prepared core material is covered with separating layer in a fluid bed with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer is sprayed as a disperssion onto the pellets covered with separating layer in a fluid bed. Enteric coating layered pellets, dibasic calcium phosphate anhydrous in granulated form, microcrystalline cellulose and magnesium stearate are mixed and compressed into tablets as described in Example 3.

Example 8

Tablets

Enteric coating layered pellets (manufacturing and composition as in Example 2)	1.00 kg
Microcrystalline cellulose	1.45 kg
Anhydrous lactose	0.14 kg
Starch	0.23 kg
Povidone	0.18 kg
Purified water	0.836 kg

Povidone is dissolved in water. Microcrystalline cellulose, anhydrous lactose and starch are dry-mixed. The povidone solution is added while wet-mixing. The wet mass is dried in an oven. The granulated mass is milled using an oscillating granulator.

Enteric coating layered pellets and the prepared granulate are mixed and compressed into engraved and scored tablets using a rotary tableting machine equipped with 16 pairs of oval, 8.5x17 mm, tablet punches.

Example 9

Over-coating layer

Enteric coating layered pellets (manufacturing and composition as in Example 7)	400 g
Hydroxypropyl methylcellulose	120 g
Purified water	2 280 g

Tablets

Over-coating layered pellets	100 g
Microcrystalline cellulose	233 g

In a fluid bed apparatus a hydroxypropyl methylcellulose solution is sprayed onto enteric coating layered pellets. The Vickers hardness on the enteric coating layered pellets before applying the over-coating layer is 2 and the Vickers hardness measured on the over-coating layered pellets is 11. Pellets covered with over-coating layer and microcrystalline cellulose are mixed and compressed into tablets as described in Example 2.

Example 10

Core material

5-Fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole magnesium	150 g
Sugar sphere seeds	200 g
Hydroxypropyl methylcellulose	75 g
Purified water	1 500 g

Separating layer

Core material	380 g
Hydroxypropyl cellulose	38 g
Talc	65 g
Magnesium stearate	5 g
Purified water	760 g

Enteric coating layer

Pellets covered with separating layer	150 g
Methacrylic acid copolymer	60 g

Triethyl citrate	18 g
Mono- and diglycerides	3 g
Polysorbate 80	0.3 g
Purified water	117 g

Tablets

Enteric coating layered pellets	90 g
Microcrystalline cellulose	209 g
Sodium stearyl fumarate	1 g

Suspension layering is performed in a fluid bed apparatus. 5-Fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole magnesium is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

The prepared core material is covered with separating layer in a fluid bed apparatus. The enteric coating layer is sprayed as a water dispersion onto the pellets covered with separating layer in a fluid bed apparatus.

Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets using a single punch tableting machine using 8 mm round punches. Tablet hardness measured on a Schleuniger hardness tester is determined to 95 - 109 N.

Example 11

Enteric coating layer

Core material (no separating layer)	500 g
Methacrylic acid copolymer	500 g
Triethyl citrate	150 g
Mono- and diglycerides	25 g
Polysorbate 80	2.5 g
Purified water	978 g

Tablets

Enteric coating layered pellets	800 g
Microcrystalline cellulose	1 860 g
Sodium stearyl fumarate	7 g

Core material is produced as in Example 7.
Enteric coating layered pellets and tablet excipients are compressed as described in Example 3.

Example 12

Enteric coating layer

Pellets covered with separating layer	200 g
Hydroxypropyl methylcellulose acetate succinate	150 g
Triethyl citrate	55 g
Ethanol	1 200 g
Purified water	300 g

Tablets

Enteric coating layered pellets	300 g
Microcrystalline cellulose	700 g

The pellets covered with separating layer are produced according to Example 10.
The enteric coating layer is sprayed as a solution onto the pellets.
Enteric coating layered pellets and microcrystalline cellulose are mixed and compressed into tablets as described in Example 1.

Example 13

Core material

(+)-5-Fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole magnesium	200 g

Sugar sphere seeds	200 g
Hydroxypropyl cellulose	75 g
Purified water	1 500 g

Separating layer

Core material	380 g
Hydroxypropyl cellulose	38 g
Talc	65 g
Magnesium stearate	5 g
Purified water	760 g

Enteric coating layer

Pellets covered with separating layer	200 g
Methacrylic acid copolymer	150 g
Triethyl citrate	45 g
Mono- and diglycerides	4 g
Polysorbate 80	0.4 g
Purified water	300 g

Tablets

Enteric coating layered pellets	100 g
Microcrystalline cellulose	250 g
Sodium stearyl fumarate	1 g

Suspension layering is performed in a fluid bed apparatus. (+)-5-Fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole magnesium is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

The prepared core material is covered with separating layer in a fluid bed apparatus. The enteric coating layer is sprayed as a water dispersion onto the pellets covered with separating layer in a fluid bed apparatus.

Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets using 10 mm round punches.

Example 14

Enteric coating layer	
Pellets covered with separating layer	200 g
Methacrylic acid copolymer	200 g
Triethyl citrate	60 g
Mono- and diglycerides	10 g
Polysorbate 80	1 g
Purified water	391 g
Over-coating layer	
Enteric coating layered pellets	471 g
Hydroxypropyl methylcellulose	6 g
Magnesium stearate	0.2 g
Purified water	120 g
Tablets	
Over-coating layered pellets	140 g
Microcrystalline cellulose	114 g
Sodium stearyl fumarate	0.4 g

Pellets covered with separating layer are produced according to Example 13. The enteric coating layer and the over-coating layer are sprayed onto pellets in a fluid bed apparatus. Over-coating layered pellets and tablet excipients are compressed using a single punch (round, 12 mm) tableting machine.

Example 15

Enteric coating layer	
Pellets covered with separating layer	200 g
Methacrylic acid copolymer	40 g
Triethyl citrate	12 g
Mono- and diglycerides	2 g
Polysorbate 80	0.2 g
Purified water	78 g

Over-coating layer	
Enteric coating layered pellets	200 g
Hydroxypropyl methylcellulose	4 g
Magnesium stearate	0.1 g
Tablets	
Over-coating layered pellets	69 g
Microcrystalline cellulose	230 g
Sodium stearyl fumarate	0.7 g

Pellets covered with separating layer are produced according to Example 13. The enteric coating layer and the over-coating layer are sprayed onto pellets in a fluid bed apparatus. The amount of enteric coating layer material used in this example corresponds to an enteric coating layer thickness of approx. 20 µm. Over-coating layered pellets and tablet excipients are compressed using a single punch (round, 10 mm) tableting machine.

Example 16

Enteric coating layer	
Pellets covered with separating layer	500 g
Cellulose acetate phtalate	375 g
Diethyl phthalate	150 g
Acetone	2 000 g
Ethanol	2 000 g
Tablets	
Enteric coating layered pellets	100 g
Microcrystalline cellulose	300 g
Crospovidone	8 g
Sodium stearyl fumarate	1 g

The pellets covered with separating layer are produced as in Example 13.

The enteric coating layer is applied in a fluid bed from a acetone/ethanol solution. Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets as described in Example 2.

Example 17

Core material	
5-Carbomethoxy-6-methyl-2[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole	200 g
Sugar sphere seeds	200 g
Hydroxypropyl cellulose	25 g
Purified water	623 g
Separating layer	
Core material	200 g
Hydroxypropyl cellulose	20 g
Talc	34 g
Magnesium stearate	3 g
Purified water	457 g
Enteric coating layer	
Pellets covered with separating layer	200 g
Methacrylic acid copolymer	150 g
Triethyl citrate	45 g
Mono- and diglycerides	8 g
Polysorbate 80	1 g
Purified water	250 g
Tablets	
Enteric coating layered pellets	100 g
Microcrystalline cellulose	232 g
Sodium stearyl fumarate	1 g

Suspension layering is performed in a fluid bed apparatus using bottom spray technique. 5-Carbomethoxy-6-methyl-2[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole is sprayed onto sugar sphere seeds from a

water solution containing the dissolved binder.

The prepared core material is covered with separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer is sprayed as a water dispersion onto the pellets covered with separating layer in a fluid bed apparatus.

Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets using a single punch tableting machine (Korsch EK0) using 11 mm round punches. Tablet hardness measured on a Schleuniger hardness tester is determined to approx. 170 N.

Example 18

The same tableted dosage form as described in Example 17 is produced with (+)-5-carbomethoxy-6-methyl-2[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium as active substance.

The results from tests on acid resistance of the enteric coating layered pellets and the compressed tablets are disclosed in Table I, below.

Table I

Example No	Acid resistance, pellets (%)	Acid resistance, tablets (%)
1	95	93
10	95	86

Comments:

Surprisingly, the acid resistance, tablets, shows that the enteric coating layer according to the present invention sufficiently withstands compression.

Reference example I

Tablets

Omeprazole enteric coating layered pellets	180 g
Microcrystalline cellulose	219 g
Sodium stearyl fumarate	1 g

Omeprazole pellets from Losec® 40 mg capsules are mixed with microcrystalline cellulose and sodium stearyl fumarate and compressed into tablets using a single punch tableting machine. The Vickers hardness on the enteric coating layered pellets is measured to a value of 22. The tablet tooling is round with a diameter of 10 mm. Punch force is set to 3.7 kN.

Reference example II

Tablets

Lansoprazole enteric coating layered pellets (content of Lanzo® 30 mg capsules)	276 g
Microcrystalline cellulose	644 g

Lansoprazole pellets are mixed with microcrystalline cellulose and tableted in a single punch tableting machine. The Vickers hardness on enteric coating layered pellets is measured to a value of 18. The tablet tooling is round with a diameter of 12 mm. Punch force is set to 3.6 kN.

Reference example III

Core material

Magnesium omeprazole	15.0 kg
Sugar sphere seeds	15.0 kg
Hydroxypropyl methylcellulose	2.25 kg
Purified water	40 kg

Separating layer	
Core material	15.0 kg
Hydroxypropyl cellulose	1.5 kg
Talc	2.57 kg
Magnesium stearate	0.21 kg
Purified water	30 kg

Enteric coating layer	
Pellets covered with separating layer	200 g

Enteric coating layer material is used as described in Drugs Made In Germany 37, No. 2 (1994), p.53, Table 1, Formulation no. 9.
The amount of coating polymer as calculated in above reference is 40 % (w/w).

Over-coating layer	
Enteric coating layered pellets	291 g
Hydroxypropyl methylcellulose	4 g
Magnesium stearate	0.2 g
Purified water	80 g

Tablets	
Over-coating layered pellets	75 g
Microcrystalline cellulose	174 g
Sodium stearyl fumarate	0.6 g

Suspension layering is performed in a fluid bed apparatus. Omeprazol magnesium is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.The separating layer, enteric coating layer and the over-coating layer are sprayed onto pellets in a fluid bed apparatus. The over-coating layer is applied to prevent sticking of pellets before tableting. Over-coating layered pellets and tablet excipients are tableted as in Example 2. Upper punch force is set to 5 kN.

The results from tests on acid resistance of the enteric coating layered pellets and the compressed tablets are disclosed in Table II, below.

Table II

Reference example number	Acid resistance pellets (%),	Acid resistance tablets (%),
I	97	6
II	98	25
III	98	82

Comments:

As can be seen from the presented data, the enteric coating layer of the products studied, including the two marketed products (Reference examples I and II) do not possess the mechanical properties required to withstand compression into tablets.

Preparation of active substance

5-Fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole magnesium and 5-carbomethoxy-6-methyl-2[[(3,4-demethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole used in the examples are disclosed in WO 90/06925 and WO 91/19712, hereby incorporated as a whole by references. Some of the single enantiomers thereof are prepared in accordance with the following Examples A - E.

Example A. Preparation of (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

The crude product of the diastereomers of a mixture of two regioisomeric mandelic esters, namely 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (5.0 g, 9.8 mmol) were divided into five parts and each part was chromatographed on a reversed phase column (HPLC, Kromasil C8) in order to separate the diastereomers. The stereo isomers were easily separated by elution with a mixture of aqueous 0.1 M ammonium acetate and acetonitrile (67.5/32.5). However each separated diastereomer consisted of a mixture of the two regioisomers. These intermediates were used directly in their

solutions during the hydrolysis step. To the acetonitrile/aqueous solutions of the more lipophilic diastereomer were added 1 M aqueous solutions of NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH_4Cl whereupon the solutions from each preparation were combined and extracted with methylene chloride. The organic phases were dried over Na_2SO_4 and the solvents were removed by film evaporation. Addition of 30 ml of acetonitrile afforded the product to crystallize and after filtration there was obtained 260 mg (16%) of the title compound as white crystals, m.p. 152°-154°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was 99.2%. [a $]^{20}_D$= +208.6° (c=0.5%, chloroform).

Example B. Preparation of (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

Magnesium (7.1 mg, 0.29 mmol) is dissolved and reacted with methanol at 40°C with a catalytic amount of methylene chloride. The reaction is run under nitrogen and is finished after two hours. (+)-5-Fluoro-2-[[(4-cyclo-propylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (200 mg, 0.58 mmol) obtained as in Example A was added after the magnesium methoxide solution had been chilled to room temperature. The mixture is stirred for two hours whereupon a small amount of water (0.05 ml) is added. After stirring another hour the small amount of inorganic salts are filtered off. The solution is concentrated on a rotavapor until two ml of the solution is left. While chilling and stirring, water is added dropwise which afforded the product to precipitate. After filtration the product is ished with a small amount of water and then dried in vacuum. There is obtained 97 mg (47%) of the title compound as a white powder. [a]$^{20}_D$= +191.3° (c=1.0%, DMSO).

Example C. Preparation of (+)-5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

The crude product of the diastereomers of a mixture of two regioisomeric mandelic esters, namely 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (1.8 g, 3.3 mmol) was divided into three parts. Each part was chromatographed on a reversed phase column (HPLC, Kromasil C8) in order to separate the diastereomers. The

stereoisomers were easily separated by elution with a mixture of aqueous 0.1 M ammonium acetate and acetonitrile (70/30), but each separated diastereomer consisted of a mixture of the two regioisomers. These intermediates were used directly in their solutions during the hydrolyses; To the acetonitrile/aqueous solutions of the more lipophilic diastereomer were added 1 M aqueous solutions of NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH_4Cl. The solutions from each preparation were combined and extracted with methylenechloride whereupon the organic phases were dried over Na_2SO_4. Removal of the solvents and flash chromatography of the residue (silica gel, methanol-methylenechloride gradient 1-8%) yielded 250 mg of a yellow oil. The product was crystallised by adding acetonitrile (3 ml) and after filtration there was obtained 210 mg (32%) of the title compound as white crystals m.p. 171-173° C. $[a]^{20}_D$= +153.1° (c=0.5%, chloroform).

Example D. Preparation of (+)-5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

To a mixture of (+)-5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1-H-benzimidazole (200 mg, 0.51 mmol) and ethanol (10 ml) was added an aqueous solution of 2.0 M NaOH (0.26 ml, 0.51 mmol). The solvent was removed by film evaporation whereupon the residue was dissolved in 2-butanone (1 ml). Toluene (5 ml) was added dropwise while stirring. The formed precipitate was removed by centrifugation and washed with diethyl ether. There was obtained 170 mg (81%) of the title compound as white crystals m. p. (decomp.) 170°-173°C. $[a]^{20}_D$= +93.6°(c=1%, methanol).

Example E. Preparation of (+)-5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

(+)-5-Carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole sodium salt (100 mg, 0.24 mmol) obtained as in Example D is dissolved in water (2 ml) and $MgCl_2x6H_2O$ (25 mg, 0.12 mmol) dissolved in water (1 ml) is added dropwise. The formed precipitate is isolated by centrifugation and ished with water. The product is dried in a desiccator and there is obtained 84 mg (87%) of a white powder. $[a]^{20}_D$= + 170° (c=0.5%, DMSO).

CLAIMS

1. An oral pharmaceutical multiple unit tableted dosage form comprising tablet excipients and individually enteric coating layered units of a core material containing active substance in the form of 5-fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole or 5-carbomethoxy-6-methyl-2[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole or one of its single enantiomers or an alkaline salt thereof, optionally mixed with alkaline compounds, covered with one or more layer(s) of which at least one is an enteric coating layer, whereby the enteric coating layer has mechanical properties such that the compression of the individual units mixed with the tablet excipients into the multiple unit tableted dosage form does not significantly affect the acid resistance of the individually enteric coating layered units.

2. A tableted dosage form according to claim 1, wherein the active substance is 5-fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or one of its single enantiomers or an alkaline salt thereof.

3. A tableted dosage form according to claim 1, wherein the active substance is 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or one of its single enantiomers or an alkaline salt thereof.

4. A tableted dosage form according to claim 1, wherein the acid resistance of the individually enteric coating layered units is in coherence with the requirements on enteric coated articles defined in the United States Pharmacopeia.

5. A tableted dosage form according to claim 1, wherein the acid resistance of the individually enteric coating layered units does not decrease more than 10 % during the compression of the individual units into the multiple unit tableted dosage form.

6. A tableted dosage form according to claim 1, wherein the enteric coating layer covering the individual units comprises a plasticized enteric coating layer material.

7. A tableted dosage form according to claim 1, wherein the enteric coating layer covering the individual units has a thickness of at least 10 µm.

8. A tableted dosage form according to claim 1, wherein the individually enteric coating layered units are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.

9. A tableted dosage form according to claim 1, wherein the dosage form is divisible.

10. A tableted dosage form according to claim 1, wherein the dosage form is dispersible to a suspension of individually enteric coating layered units in an aqueous liquid.

11. A tableted dosage form according to claim 1, wherein an optionally applied separating layer(s) comprises pharmaceutically acceptable excipients which are soluble, or insoluble but disintegrating in water, and optionally alkaline compounds.

12. A tableted dosage form according to claim 1, wherein the core material is a seed layered with the active substance.

13. A tableted dosage form according to claim 12, wherein the seeds have a size of 0.1 - 2 mm.

14. A process for the manufacture of a pharmaceutical multiple unit tableted dosage form comprising tablet excipients and individually enteric coating layered units of a core material containing active substance as defined in clam 1, optionally mixed with alkaline compounds, wherein the core material is optionally covered with one or more separating layer(s) and further covered with one or more enteric coating layer(s), whereafter the individually enteric coating layered units are mixed with tablet excipients and compressed into a tablet, and whereby the enteric coating layer has mechanical properties such that the compression of the individual units with the tablet excipients into the multiple unit tableted dosage form does not significantly affect the acid resistance of the individually enteric coating layered units.

15. A process according to claim 14, wherein the individually enteric coating layered units are further coated with an over-coating layer before compression of the individual units into the multiple unit tableted dosage form.

16. A tableted dosage form according to any of claims 1 to 13 for use in therapy.

17. A tableted dosage form according to any of claims 1 to 13 for use in inhibiting gastric acid secretion in mammals and man.

18. A tableted dosage form according to any of claims 1 to 13 for use in the treatment of gastrointestinal inflammatory diseases in mammals and man.

19. A method for inhibiting gastric acid secretion in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 13.

20. A method for the treatment of gastrointestinal inflammatory diseases in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims

1 to 13.

21. A press-through blister package comprising a multiple unit tableted dosage form according to any of claims 1 to 13.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00680

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/26, A61K 9/20, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87), page 5, line 6 - page 9, line 12, examples --	1-18,21
X	EP 0519144 A1 (ILSAN ILAC VE HAMMADDELERI SANAYI A.S.), 23 December 1992 (23.12.92) --	1-18,21
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90), page 3, line 37 - line 55 --	1-18,21
A	WO 9222284 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 23 December 1992 (23.12.92) --	1-18,21

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 1995	21.10.1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00680

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19-20
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 95/00680

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0247983	02/12/87	SE-T3- 0247983	
		AU-B- 601974	27/09/90
		AU-A- 7191287	05/11/87
		CA-A- 1292693	03/12/91
		DE-A- 3783394	18/02/93
		DK-B- 169988	24/04/95
		EP-A,A,A 0496437	29/07/92
		EP-A,A- 0567201	27/10/93
		ES-T- 2006457	01/01/94
		GB-A- 2189698	04/11/87
		HK-A- 135294	09/12/94
		IE-B- 61416	02/11/94
		JP-C- 1863556	08/08/94
		JP-A- 5294831	09/11/93
		JP-A- 62258320	10/11/87
		NO-B,C- 174239	27/12/93
		SU-A- 1820837	07/06/93
		US-A- 4786505	22/11/88
EP-A1- 0519144	23/12/92	NONE	
EP-A1- 0365947	02/05/90	SE-T3- 0365947	
		AU-B- 612525	11/07/91
		AU-A- 4365089	03/05/90
		CA-A- 2000932	26/04/90
		DE-T- 68907177	13/01/94
		ES-T- 2055775	01/09/94
		HK-A- 123394	18/11/94
		JP-A- 2164821	25/06/90
		SE-A- 8803822	26/10/88
		US-A- 5178868	12/01/93
WO-A1- 9222284	23/12/92	AU-A- 1974692	12/01/93
		BG-A- 98286	15/08/94
		CN-A- 1067809	13/01/93
		CZ-A- 9302764	13/07/94
		DE-A- 4219390	24/12/92
		EP-A- 0519365	23/12/92
		EP-A- 0589981	06/04/94
		FI-D- 935677	00/00/00
		JP-T- 6508118	14/09/94
		NO-A,D- 934648	16/12/93